

### **REMARKS / ARGUMENTS**

Claims 69-75, 77, 78, 81-106 are currently pending in the application.

Claims 73-74 have been cancelled herein as being drawn to non-elected subject matter. However, Applicants reserve the right to pursue the subject matter of these claims, or related subject matter, in a future continuation or divisional application.

Claims 69 and 99 have been amended. No new matter has been added by way of this amendment. Support for the amendment to claim 69 can be found in the specification, *e.g.*, at page 14, lines 21-31. Claim 99 has been amended to correct a typographical error.

Applicants gratefully acknowledge the allowance of claims 78, 81, 82 and 85-87.

Following entry of this amendment, claims 69-72, 75, 77, 78, and 81-106 will be pending in this application. Applicants respectfully request reconsideration of pending claims 69-72, 75, 77, 78, and 81-106.

#### **I. Request for Withdrawal of Finality of Rejection**

Applicant's respectfully submit that the Examiner's designation of the Office Action mailed June 1, 2005 as a "Final" Office Action was premature. The Manual of Patent Examining Procedure (MPEP) states that:

Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement [IDS] filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

MPEP § 706.07(a) (emphasis added).

In the Office Action dated June 1, 2005, the Examiner introduced at least TWO new grounds of rejection that were neither necessitated by Applicant's amendment nor based on information submitted on an IDS.

At the outset, Applicants wish to point out that in the Office Action dated October 6, 2004, the Examiner indicated that claims 70-72 would be allowable if rewritten in independent form (page 11). As such, new claims 97-99 were added (see Response dated March 7, 2005, page 14), which were identical to claims 70-72 rewritten in independent form.

In the current Office Action dated June 1, 2005, the Examiner has now rejected claims 97-99 under 35 U.S.C. § 112, first paragraph (written description) and also rejected claims 98-99 under 35 U.S.C. § 112, second paragraph, for recitation of the word "interaction" (see discussion below).

Thus, in the current Office Action dated June 1, 2005, the Examiner introduced TWO new grounds of rejection that were neither necessitated by Applicant's amendment nor based on information submitted on an IDS, which is contrary to MPEP § 706.07(a). Applicants submit that the Examiner could have raised each of these rejections previously instead of informing the Applicants that these claims (claims 70-72) would be allowable if rewritten in independent form (claims 97-99).

Accordingly, Applicants respectfully submit that the finality of rejection be withdrawn, *inter alia*, to give the Applicants an adequate chance to reply to the Examiner's TWO new grounds of rejection regarding claims 97-99.

**I. Objection to the Specification**

In response to the Examiner's objection to the specification, Applicants have amended the specification to capitalize trademarks. No new matter has been added by way of this amendment.

Accordingly, Applicants respectfully request that these objections to the specification be reconsidered and withdrawn.

**II. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)**

The Examiner has made a number of rejections under 35 U.S.C. § 112, first paragraph regarding alleged lack of written description. For clarity, each of these rejections will be discussed separately.

**A. Claims 69-72 and 77**

The Examiner has rejected claims 69-72 and 77 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, pages 3-4).

Applicants respectfully traverse this ground of rejection.

The Examiner opines that the applicants have

[have] not demonstrated...possession of the large number of fragments encompassed in the claims or provide [*sic*] a representative number of species for the large genus contained in the claims. A skilled artisan cannot envision the detailed chemical structure of the claims because there is no description as to a conserved region or what composition of amino acids is present or absent in SEQ ID NO:2.

(Office Action, page 4)

As the Examiner is aware, the written description requirement of 35 U.S.C. § 112, first paragraph, does not require a description of the complete structure of every species within a chemical genus. See, *e.g.*, *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) (“A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.”) A “description of a genus of cDNAs may be achieved by means of... a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). Additionally, “the written description requirement can be met by ‘show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...*i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002) (emphasis added). While the claims recite

polypeptides, and not DNA as in *Lilly* and *Enzo*, the same standard applies. See *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916 (Fed. Cir. 2004) (“We agree with Rochester that *Fiers*, *Lilly*, and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester’s position. It is irrelevant, the statute applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue.”)

Here, the complete structure of SEQ ID NO:2 is described, and the polypeptides in the genus recited in claims 69-72 and 77 share at least 80% identity with the structure of SEQ ID NO:2. Thus, the structural features that are common to the genus make up at least 80% of the structure set forth in SEQ ID NO:2. Respectfully, the Examiner has not adequately explained why this degree of structural similarity is inadequate to constitute a “substantial portion of the genus,” as required in *Lilly*. In addition to the identity to SEQ ID NO:2, dependent claims 70-72 also recite a particular Smurf activity (or function) that is being detected in the claimed methods, which further supplement the requirements of *Lilly*.

However, solely in an effort to advance prosecution of this application, claim 69 has been amended to recite that the Smurf activity detected is the activity of a Smurf comprising a WW domain and/or a HECT domain and comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2. As amended, the claims now recite a genus that both shares at least 80% identity with the structure of SEQ ID NO:2 and contains a WW and/or Hect domain. Thus, as suggested by the Examiner, independent claim 69 now recites “a conserved region” and “what composition of amino acids is present or absent in SEQ ID NO:2.”

Thus, Applicants submit that claim 69, as amended herein, complies with all the requirements of 35 U.S.C. § 112, first paragraph. Similarly, claims 7-72 and 77, which depend either directly or indirectly on claim 69, as amended herein, and thus contain all the limitations thereof, also comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

**B. Claims 69-72, 77 and 88-91**

The Examiner has rejected claims 69-72, 77, and 88-91 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, pages 4-5).

Applicants respectfully traverse this ground of rejection.

The Examiner directs Applicants to the passage on page 21, lines 33-35 of the specification and opines that there is no written support for “80% identity with the amino acid sequence depicted in SEQ ID NO:2.” The passage states that:

two amino acid sequences are “substantially homologous” or “substantially similar when greater than 70% of the amino acid sequences are identical, or greater than about 90% are similar (functionally similar).

(page 21, lines 33-35; emphasis added).

The specification defines the term “about” to mean “within 20%, preferably within 10% and more preferably within 5% of a given range” (page 16, lines 6-7; emphasis added). Thus, “about 90%” means, *inter alia*, 90% ± 10% (*i.e.*, 80%). Thus, contrary to the Examiner’s assertions, “80% identity” is expressly disclosed in the specification.

Accordingly, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

**C. Claims 92-106**

The Examiner has rejected claims 92-106 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, pages 5-7).

Applicants respectfully traverse this ground of rejection.

At the outset, Applicants wish to point out that in the Office Action dated October 6, 2004, the Examiner indicated that claims 70-72 would be allowable if rewritten in independent form (page 11). As such, new claims 97-99 were added (see Response dated March 7, 2005, page 14), which were identical to claims 70-72 rewritten in independent form. In the current Office Action dated June 1, 2005, the Examiner has now rejected claims 97-99 under 35 U.S.C. § 112, first paragraph. Applicants believe this rejection was made in error and request clarification.<sup>1</sup>

The Examiner opines that “the claims do not specify what Smurf protein is being monitored, for example, provide a reference structure [*sic*]” (Office Action, page 5). The Examiner then provides a number of quotations, which seem to indicate that the Examiner requires a “chemical structure of the encompassed genus of polypeptides” (see, *e.g.*, Office Action, pages 6-7).

Independent claims 92, 93, 97 and 98 all recite methods of screening for a modulator of Smurf activity, and not necessarily Smurf proteins *per se*, as the Examiner seems to indicate. Each of these claims specifically sets forth the particular Smurf activity being screened for, *e.g.*, ubiquitination of a Smad polypeptide (claims 92, 94, and 97, 104), ubiquitination of a TGF $\beta$  receptor (claim 93, 95, 96 and 105), and interaction of a Smurf WW domain with a PPXY domain of a Smad polypeptide (claim 98, 99-101, and 106).

The specification discloses two Smurf polypeptides, Smurf1 and Smurf2, which can be used in the screening methods of the invention. Smurf2 is closely related to Smurf1, but possesses an extra WW domain downstream of the C2 domain (page 58, lines 21-22). Additionally, Smurf2 displays approximately 75% homology to the amino acid sequence of Smurf1 (page 58, lines 18-20) and an even higher sequence homology when compared on a domain-by-domain basis (see Figure 13). Each of Smurf1 and Smurf 2 has at least two WW domains, one C2 domain and one HECT domain (page 10, lines 4-6; page 58, lines 21-22; and Figure 13). Moreover, each of Smurf1 and Smurf2 is capable of interacting with a PPXY domain of a Smad protein (page 13, lines 13 and 23). Additionally, the specification provides

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<sup>1</sup> New claims 92-96 and 100-106 (added in the March 7, 2005 Response) were modeled after claims 97-98, which the Examiner indicated were allowable in the October 6, 2004 Office Action. Thus, for the same reasons, claims 92-96 and 100-106 should also be allowable.

extensive guidance at pages 24-27 as to how to obtain other Smurf derivatives (*e.g.*, insertions, deletions, substitutions, *etc.*), using techniques well-known to skilled artisans at the time the application was filed (*see, e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification).

Thus, for the reasons above, Applicants submit that claims 92-106, comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

### **III. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)**

Claims 69-72, 77 and 88-91 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement (Office Action, pages 7-12).

Applicants respectfully traverse this ground of rejection.

MPEP § 2164.01 states that 35 U.S.C. § 112, first paragraph, “has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.” The same section further states that “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”

Applicants submit that one of ordinary skill in the art would know how to identify and utilize Smurf polypeptides for use in the methods of the invention without undue experimentation. For example, the specification provides extensive guidance as to how to clone Smurf family genes (*e.g.*, at pages 23-24) and express Smurf family proteins (*e.g.*, at pages 27-39). The Examiner is also directed to Example 1, wherein human, mouse and *Xenopus* Smurf1 were identified, and to Example 2, wherein human and mouse Smurf2 were identified using techniques disclosed in the specification and well-known in the art. Additionally, the specification provides extensive guidance at pages 24-27 as to how to obtain Smurf derivatives (*e.g.*, insertions, deletions, substitutions, *etc.*), using techniques well-known to skilled artisans at the time the application was filed (*see, e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification) Further, the specification provides

additional guidance at pages 41-46 as to how to use the Smurf family proteins in various routine *in vitro* and *in vivo* screening assays.

The Examiner also opines that the “amount of experimentation necessary to practice the claimed invention is undue as the claims encompass an unspecified amount of peptide fragments. The instant specification indicates that ‘Smurf proteins of the invention may contain at least about 5 and preferably at least 10 contiguous amino acids from the sequences set forth in SEQ ID NOS:2/4’ (see page 4)...However, the specification does not demonstrate any fragments of the claimed sequence having Smurf activity.” (Office Action, page 8).

However, Applicants respectfully submit that Applicants have enabled SEQ ID NOS: 2 and 4 and fragments thereof by providing the complete amino acid sequence of SEQ ID NOS:2 and 4. Respectfully, the Examiner has provided no reasoning for her conclusion that other fragments of SEQ ID NOS: 2 or 4 could not be similarly used in the methods of the claimed invention. Even if some of the species in a genus claim are inoperative, the claims are not necessarily invalid. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576; 224 U.S.P.Q. (BNA) 409. “It is not a function of the claims to specifically exclude...possible inoperative substances....” *Id.* (citing *In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 U.S.P.Q. (BNA) 46, 48 (CCPA 1974) (emphasis omitted); *accord, In re Geerdes*, 491 F.2d 1260, 1265, 180 U.S.P.Q. (BNA) 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 U.S.P.Q. (BNA) 331, 334-35 (CCPA 1973)).

The Examiner further opines that a “large quantity of experimentation would be necessary to generate the infinite number of fragments recited in the claims and possibly screen same [*sic*] for functional activity” (Office Action, page 9). However, it was routine at the time the application was filed to screen large amounts of mutants, for example in high-throughput screening assays, for functional activity. See, *e.g.*, MPEP § 2164.01 (“[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”).

Thus, Applicants submit that claims 69-72, 77 and 88-91 are enabled and comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.



**IV. Rejection Under 35 U.S.C. § 112, Second Paragraph**

The Examiner has rejected claims 83-94 and 98-99 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for the recitation of the term “interaction” (Office Action, page 13).<sup>2</sup>

Applicants respectfully traverse this ground of rejection.

As the Examiner noted, claim 83, for example, recites that Smurf activity is interaction of a Smurf WW domain with a PPXY domain. The Examiner opines that it is unclear how the two domains are interacting (Office Action, page 13).

Respectfully, one skilled in the art would recognize that when two domains “interact” they associate or bind with one another. This is consistent with the use of “interact,” “interactions” and similar terms throughout the specification. See, for example, page 14, lines 21-31; page 25, lines 18-26; page 32, lines 10-16; page 46, lines 13-24; page 52, line 24 - page 53, line 27.

Thus, Applicants submit that the term “interaction” is definite, and reconsideration and withdrawal of this ground of rejection is respectfully requested.

**V. Conclusion**

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If the Examiner does not agree, then Applicants submit that, at the very least, the finality of this rejection should be withdrawn for the reasons discussed in Section I above. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

This Response is being submitted within three months of the mail date of the June 1, 2005 Office Action. Thus, Applicants believe no fees are due in connection with this Amendment. However, if any fees are due, please charge them to Deposit Account 50-3013.

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<sup>2</sup> Applicants note that this new ground of rejection was not previously made with respect to claims 70-72, which were held to be allowable in the prior October 6, 2004 Office Action if re-written in independent form. As such, new claims 97-99 were added in the Response dated March 7, 2005.

If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition filed concurrently herewith, such an extension is requested and the fee should be charged to the same Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

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Date: Aug. 30, 2005

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